On the Physiological Action of a Recently-Discovered African Arrow Poison.

By CHARLES BOLTON, M.D., Assistant Physician to University College Hospital.

(Communicated by Professor Sidney Martin, F.R.S. Received March 20,—Read April 5, 1906.)

(From the Pathological Laboratory, University College, London.)

The investigation of the toxic properties of this poison was undertaken at the request of Professor Ray Lankester, to whom it was sent by Dr. David Alexander of the West African Medical Staff Corps in September, 1904.

Dr. Alexander obtained the poison from a medicine house at Ghasi, a pagan town on the Gongola River, a tributary of the Benue, in Northern Nigeria. He states that when fresh it is a semi-fluid, black, sticky substance, that it is smeared on sticks, and that when it is required for re-dipping the arrows it is scraped off and heated. It appears to be composed of, or at all events to contain, the juice of a variety of Fig, and it is stated that placenta is used in its manufacture. Dr. Alexander further states that he saw a native shot in the abdomen with a poisoned arrow, and that death resulted apparently from heart failure in about 25 minutes.

No attempt has yet been made to analyse the substance chemically, and the following remarks therefore apply entirely to its physiological action. There are many further points in relation to the action of this interesting poison which require elucidation, but as only a small amount was available for use it was thought advisable to publish the main results which have been obtained. The subject will be treated of under the following headings:—

1. Physical properties of the poison.
2. Minimum fatal dose.
3. Symptoms following its injection into animals.
4. *Post-mortem* appearances resulting from such injection.
5. Experimental investigation into the physiological action of the poison.
6. Conclusions.
7. Protocol of experiments.

1. PHYSICAL PROPERTIES OF THE POISON.

The poison which I received was smeared on two canes and dusted over with the powder from the inside of a gourd to preserve it. The substance was easily scraped off and found to be soft, pasty, black, somewhat granular in appearance, and possessed of a peculiar sweet smell. It dissolved quite easily in water, forming a dark greenish-brown muddy solution with a slightly acid reaction.

On centrifugalisation or filtration a greenish-brown mud, chiefly composed of starch grains, was separated, leaving a clear transparent dark brown solution. Boiling for half an hour does not affect the action of the solution.

The poison was dissolved in 0·86-per-cent. salt solution for intravenous injection into animals.

2. FATAL DOSE IN THE CASE OF THE RABBIT.

The solution was injected into the marginal vein of the ear in each case.

Single doses:—

gramme.		
0·15	per kilogramme weight of animal killed in	3 mins.
0·112	,, ,, ,,	3 ,,
0·094	,, ,, ,,	4 ,,
0·072	,, ,, ,,	4 ,,
0·065	,, ,, ,,	4 ,,
0·05	,, ,, ,,	10 ,,
0·031	,, ,, ,,	2½ hrs.
0·027	Completely recovered.	

Repeated doses:—

gramme.			
0·029	per kilogramme weight of animal killed in	2 hrs.	(as a 2nd dose).
0·029	,, ,, ,,	20 mins.	(as a 2nd dose).
0·027	,, ,, ,,	15 ,,	(as a 3rd dose).
0·019	,, ,, ,,	20 ,,	(as a 4th dose).

The minimum lethal dose is therefore about 0·03 gramme per kilogramme weight, but much smaller doses (*e.g.*, 0·019) will kill if the animal has been injected on previous days.

3. SYMPTOMS FOLLOWING INJECTION OF THE POISON.

Rabbit.—There are four obvious symptoms:—

(1) Movements of the jaws, tongue, and nose; (2) dyspnœa; (3) muscular weakness; (4) restlessness and often a slight convulsion immediately before death.

With large doses of the poison injected intravenously the symptoms begin almost at once or from one or two minutes after injection. The first symptoms are licking movements and twitching of the alæ nasi, the jaws being moved as if the animal were trying to chew or swallow; sometimes it puts up its fore paw as if endeavouring to remove something from the mouth. Occasionally salivation occurs. Attacks of inspiratory dyspnœa then come on, the animal opening its mouth and stretching its neck in inspiration, and these alternate with periods of rapid shallow breathing. A general muscular weakness now prevails; the head sinks down, and the animal finally collapses and lies panting on its side. It sometimes tosses itself about in its efforts to hop, or rolls over and staggers about. Finally, a slight convulsion, in which the animal stretches itself out, occurs during the death agony.

After very small doses the only sign of poisoning may be a single attack of dyspnœa, or more prolonged and laboured breathing with movements of the jaws and tongue may occur, and the animal may subsequently recover without any weakness supervening. On auscultation of the chest air is heard to enter the lungs quite well, and the heart, as a rule, is rapid, but on one occasion for a while it was slow and irregular in rhythm.

Cat.—Similar symptoms are observed with intravenous injections as in the case of the rabbit, and they come at the same time, *e.g.*, salivation, licking, and chewing movements, the saliva being churned up into a foam, with coughing and retching, but no vomiting. Dyspnœa, inspiratory or shallow and rapid, and muscular weakness then supervene, and during a convulsion in which fæces are voided death occurs.

Guinea-pigs.—After intraperitoneal or subcutaneous injection of an amount sufficient to kill a rabbit the symptoms commence after about half an hour, and in one hour they are well marked. The animal lies on its abdomen, and on trying to move violent trembling comes on, and it staggers about. There is marked loss of power in the legs, especially the front legs, and the head sinks down as if too heavy for the muscles to support. For some time the animal can move along by means of its hind legs, but finally they become completely powerless, and it lies on its side breathing rapidly. The respirations become slower, and after a few gasps it dies. No convulsions or twitchings occur. Death takes place in about one and a half hours.

4. *Post-mortem* APPEARANCES.

The only abnormal appearances found after death are seen in the heart and large blood vessels, and these indicate that death has occurred from heart failure. The remaining organs of the body have invariably been found normal.

Heart.—This organ is flabby and dilated in both its left and right sides. Its cavities are full of blood, dark in colour in the right ventricle and bright red in the left ventricle. The large vessels are also full of blood. The heart evidently stops in diastole.

As a *post-mortem* phenomenon the left ventricle may pass into systole.

If the unfiltered or uncentrifugalised solution has been injected in large doses, the blood in all the cavities of the heart is liable to be found clotted immediately after death, the clot being black in the right cavities and red in the left cavities. The large veins are full of dark clot, and the aorta contains bright red clot. The clotting extends up to the jugular veins. The pulmonary vessels contain fluid blood, and the portal vein may contain a few clots, but here the blood as a whole is fluid.

If the solution has been centrifugalised or filtered previous to injection no clotting occurs. In all cases the blood clotted normally when removed from the body. In one case which had received four injections extending over a period of six days evidence of a gradual heart failure was found in the presence of dropsy of the mediastinum and slight bilateral hydrothorax.

Central Nervous System.—The spinal cord and bulb were stained by Nissel's method in one case, which had received several injections of the poison extending over a period of several days. The nerve cells were normal in all parts.

5. MODE OF ACTION.

In this investigation the animals used were cats and rabbits. Ether was in all cases administered before and during the experiments.

Neither morphia nor curari was previously administered as it was thought that it would be better to rely entirely upon ether, and the results have justified this procedure. In three cases the initial blood pressure was very high, probably owing to the ether, but this did not interfere with the results, because the relative readings of the blood pressure before and after injection were only required and not the absolute readings.

The mean arterial blood pressure was taken in either the carotid or femoral artery and recorded by means of Brodie's modified kymograph. The tube used to connect the artery with the mercurial manometer was filled with a solution of $MgSO_4$ (sp. gr. 1046). The respirations were also recorded by means of a tambour, and the time marked in seconds.

Artificial respiration was employed through a tracheotomy tube in the spinal-cord experiments, the air being blown through a bottle containing ether. A secondary coil and bichromate battery were used for the stimulation experiments.

A tracing of the normal blood pressure and of the respiration was taken in all cases before the poison was injected. This substance was injected either into the femoral or jugular vein in the cats and into the marginal vein of the ear in the rabbits.

The poison was also tested with regard to its action upon the frog's heart and voluntary muscle. The solutions were made with Ringer's solution and applied with a brush. The heart beats were recorded by means of a lever in the usual way. The down-stroke represents systole.

The effects of injection of the poison upon the vascular system and respiration will first be described, after which the effects of the following procedures upon these systems under the influence of the poison will be discussed:—

Abdominal compression.
Section of vagus—
    a. Before injection of poison.
    b. After „
Excitation of vagus.
Excitation of depressor nerve.
Section of spinal cord.
Section of splanchnic nerves.
Excitation of splanchnic nerve.
Previous injection of apocodein.

Finally, the action of the poison upon the frog's heart and voluntary muscle will be considered.

Action upon the Vascular System and Respiration—Effects of the Poison alone.

Blood Pressure.—Almost immediately after the commencement of the injection, or a few seconds later, the blood pressure rises rapidly, but not suddenly. In about 10 seconds it reaches a height of about 30 to 40 mm. Hg above what it originally was. During the next few seconds the pressure curve falls a trifle, and is liable to be interrupted by sudden small depressions.

From this point there is a very slow, steady rise in the pressure, the maximum height being attained in a minute or more according to the dose. The height is now from 10 to 20 mm. Hg greater than the maximum of the first rise. From this point the pressure curve gradually falls for two minutes or more, the incline being much steeper during the last half minute.

The curve is now frequently interrupted by sudden drops in the pressure, the latter recovering itself each time less and less, till it reaches its lowest point at death. With small doses the effect is not so marked, and the final fall of pressure is very gradual, irregular small fluctuations taking place as the curve drops.

Heart.—During the first rise of pressure the rate of the heart becomes slower and the individual pulsations larger towards the end. During the slight succeeding fall the rate becomes slower still, the pulsations being larger. As the pressure curve rises the second time the rate becomes rapid, and the pulsations frequently irregular in size. As the pressure finally falls the pulsations becomes smaller, and towards the end too small to count, they are still more rapid and irregular in size and rhythm.

Respiration.—There is no effect on the respiration until the blood pressure falls towards the end, when it may become shallow.

As the heart stops, irregular respirations or large inspirations are taken. After the blood pressure has fallen to its lowest limit and there are no cardiac pulsations, inspiratory gasps may be taken at intervals for more than a minute.

It thus appears that the action of the poison is directed against the circulatory apparatus and that the effects upon the respiration are secondary. There is no evidence that respiration is directly affected; even when the voluntary muscles are paralysed the animal still breathes and gasps are taken after the heart has stopped. The blood in the left side of the heart which is found dilated is bright red, showing that asphyxia plays no part in bringing about death.

The rise of blood pressure appears to be chiefly due to vasomotor constriction, since the heart is slowed. The subsequent rapidity of the heart indicates an increased irritability, the vagus being unable to hold it in check and hence the blood pressure rises, but subsequently falls as the muscular power of the heart fails.

Effect of Abdominal Compression.

Even when the blood pressure has almost fallen to its lowest limit the heart is capable of responding to the increased amount of blood supplied to it by abdominal compression and the blood pressure rises, but if the compression is persisted in the heart fails and the blood pressure falls in spite of the compression.

This experiment illustrates the wonderful reserve power the heart possesses even when almost dead and it shows that the final fall of blood pressure is not a pure vaso-motor phenomenon, as in that case the blood pressure would be restored by abdominal compression and the heart would not suddenly fail.

There is, therefore, a direct action of the poison upon the heart muscle, the heart failure being a primary phenomenon.

Section of the Vagi.

(a) *Section before the Injection of the Poison.*—The effect of section of both vagi before the injection of the poison is to do away with the slowing of the pulse and the slight fall in the blood pressure, which occurs after the first rise in the pressure; there are in addition no depressions in the curve at this time.

The pressure gradually rises in a long curve to its maximum height and then gradually falls till death. In addition to this there is little or no increase in the pulse rate towards the end. The respiration has the usual vagus type and is unaffected by the poison, only becoming irregular as the heart stops and continuing for some time after the blood pressure has fallen.

Section of one vagus only does not produce any such alteration in the character of the curve as is produced when both vagi are divided.

Since the blood pressure rises in spite of section of both vagi, to as great an extent as it does when they are intact, the conclusion follows that the first rise of blood pressure is not due to paralysis of the vagi, and since there is no notable alteration in the pulse rate during this rise confirmatory evidence is obtained that the rise of blood pressure is chiefly due to vaso-motor constriction. The absence of slowing of the pulse during the initial rise and likewise the absence of the usual slight fall in pressure at this time when the vagi are cut, indicate that these phenomena are due to a stimulation of the vagus centre in the medulla, the effect having been abolished by section of the vagi.

I shall show later that there is no evidence whatever that the poison acts upon the central nervous system and therefore it is rendered most probable that this irritation of the vagus centre is not due to a direct action of the poison, but is merely the usual stimulation that occurs as a result of a rise of blood pressure.

(b) *Section after Injection of the Poison.*—Section of one vagus brings about a rise in the blood pressure and acceleration of the pulse at an early period whilst the blood pressure is rising, and section of the vagus on the other side does not increase this rise at a slightly later period. It is only at an early period of the injection whilst the blood pressure is rising that section of the vagus causes a further rise, section at a late period, and especially when the blood pressure is falling, bringing about no change whatever in the blood pressure curve or the rate of the heart. In one case section of the right vagus 54 minutes after injection followed by section of the left vagus 19 minutes later produced no rise at all. The section, therefore, to produce any rise in blood pressure must be done at an early period after the injection.

These results show that the vagus is certainly exerting its tonic effect upon the heart during the early stages of the poisoning and that, therefore, the first rise of blood pressure is not due to vagus paralysis but is probably of peripheral origin. Later on the vagus has lost control over the heart and its section produces no effect.

The fall of blood pressure which occurs in the later stage is, therefore, due to gradually increasing weakness of the heart muscle and not to vagus irritation.

Excitation of the Vagus.

Two effects are to be noticed:—

1. In the early stages of the rise of blood pressure excitation produces a fall of blood pressure with slowing of the heart, but the effect is usually much less than in the case of the normal animal. Before the blood pressure reaches its maximum, excitation of the vagus produces little or no effect whatever upon the blood pressure and during the final fall excitation produces no effect.

2. Instead of the pressure falling at once as it does in the normal animal on stimulation, there may be a latent period of a greater a less length which becomes longer towards the end as the vagus ceases to produce any effect. Finally prolonged stimulation produces no effect at all.

These results of excitation of the vagus point to the same conclusion as was deduced from the results of section of that nerve after injection of the poison—namely, that the vagus is exercising its tonic influence upon the heart, though to a less extent than normal, in the early periods, but that it gradually ceases to exert this tonic influence owing to increased irritability of the heart muscle, the blood pressure now rising to its maximum, and that subsequently it has lost all control over the heart.

It is more likely that the vagus is unable to hold the heart in check, owing to increased irritability of the heart muscle than that the vagus is paralysed, because prolonged stimulation of the nerve may sometimes produce an effect; if the vagus was paralysed this would not happen.

In addition to this, stimulation of the vagus may produce an effect upon the respiration, although the blood pressure is unaffected, showing that the nerve is not totally disabled, and it is unlikely that the nerve ends in the heart would be paralysed whilst those in the walls of the bronchi were unaffected.

Excitation of the Depressor Nerve.

Rabbits are used for these experiments as the depressor nerve can be isolated in that animal. Excitation of the central end of the depressor nerve at all stages of the poisoning brings about a fall of blood pressure. As the blood pressure is falling towards the end of life the effect of excitation of the depressor is liable to be less marked.

In the early stages of poisoning the depression in blood pressure may not be so marked with the same strength of stimulus as it was before the poison was injected. This result might be expected to occur as the irritability of the heart is increased. The fact that the depressor nerve will produce an effect at all stages of the poisoning shows that the central and peripheral vaso-motor nervous mechanisms are acting normally and that there is no central or peripheral nervous paralysis.

Section of the Spinal Cord.

It was found that after section of the spinal cord in the upper cervical region, the blood pressure still rose on injection of the poison to the same extent relatively as it did in the experiments with the spinal cord intact. The vaso-constriction, therefore, is obviously not of central origin.

This rise of pressure is, however, due to constriction of the peripheral vessels chiefly, because the heart by stimulation can only cause an insignificant rise of arterial pressure when the peripheral resistance is greatly diminished, as when the spinal cord is divided.

Section of the Splanchnic Nerves.

The result of section of the splanchnics is the same as that obtained in the case of section of the spinal cord. The pressure goes up as much relatively as when the splanchnics are undivided. This is confirmatory evidence of the observation that the vaso-motor action is not central.

Excitation of Splanchnic Nerve.

Stimulation of the splanchnic nerve even at a late stage of the poisoning, when the blood pressure is following, still causes a rise in the blood pressure, thus showing that the peripheral ends of the vaso-motor nerves are not paralysed.

Previous Injection of Apocodein.

Apocodein, as is well known, brings about a fall of arterial blood pressure by paralysing the terminations of the vaso-motor nerves.

After the injection of apocodein the central end of the sciatic nerve was stimulated to make certain that no rise of arterial blood pressure occurred, thus showing that the apocodein had acted upon the nerve endings. Under these circumstances, when the blood pressure had fallen as the result of the injection of apocodein, the subsequent injection of the poison still produced a marked rise in arterial blood pressure, both when the vagi were divided and when they were intact.

This result proves that the rise of blood pressure is due to a direct stimulation of the muscular coats of the arterioles. There is no evidence to show that the vaso-motor nerves are in the least affected by the poison.

Action upon the Frog's Heart.

When applied to the frog's heart the effect of the poison is to gradually diminish the size of the beats till the ventricle is brought to a stand-still in diastole, the auricle continuing to beat for a little while longer and then also stopping in diastole.

Sometimes a block is seen at the auriculo-ventricular junction, only every second beat crossing over, and occasionally irregular peristaltic waves, commencing at the base, pass over the ventricle. The ventricle may take on an independent rhythm. The rate of the heart is not altered until just before it stops, when slight slowing is noticed.

Application of atropine to the heart in arrest fails to restore its action, thus showing that the standstill is due to a direct action on the muscular tissue of the heart and not to stimulation of the terminations of the vagus. The same result is seen if the atropine is applied before the poison.

If the heart be thoroughly washed with Ringer's solution, its action may be restored, if it has not completely come to a standstill. If the sinus be stimulated with an electric current when the heart has stopped, the action may be temporarily restored.

Action upon the Voluntary Muscle of the Frog.

The poison was applied to the muscle with a brush, and at each application the muscle shortened very slightly. The nerve was stimulated with an induced current and the poison continuously applied until the muscle failed to respond to the stimulus. The muscle itself was now stimulated, and entirely failed to respond to any strength of current.

This proves that the muscular tissue itself is paralysed by the poison. The experiment, of course, does not prove that the poison does not at the same time act upon the nerve ends, but the object of this experiment was to prove whether or not the muscular tissue itself was paralysed.

6. CONCLUSIONS.

The poison selects muscular tissue for its action and there is no evidence whatever that it produces any action upon the central or peripheral nervous system. It paralyses the voluntary muscles and brings about death by a direct action upon the muscular tissue of the heart.

The first effect of the poison is to stimulate directly the muscular coats of the arterioles and thus to cause a rise of arterial pressure.

The raised arterial pressure excites the vagus centre in the medulla, and brings about a slowing of the rhythm of the heart, together with a slight fall in the arterial blood pressure. The irritability of the heart muscle is greatly increased and soon the vagus fails to hold it in check, with the result that the rhythm of the heart is accelerated and the blood pressure therefore rises to a higher level as the inhibition of the vagus is overcome. It is, however, probable that the chief factor in maintaining the high blood pressure is the constriction of the peripheral vessels.

The rhythm of the heart becomes more rapid and irregularity appears, the heart finally passing into delirium cordis and ceasing in diastole.

As the heart fails, the blood pressure falls more or less rapidly, and the fall is interrupted by rises in which the heart temporarily recovers itself. The final fall of blood pressure is due entirely to heart failure, the muscular coats of the arteries being capable of response to stimulation till the very end. Any effect upon the respiration is secondary to the effect upon the vascular system. The final convulsion is also secondary and not due to any direct action of the poison.

In the case of the frog the action of the poison is also directed towards the muscular tissue of the heart and the voluntary muscles leading to a gradual paralysis. With regard to the action on the heart, all that can be said is that the poison acts atonically on the muscular tissue like lactic acid and potash salts, and that its conductivity is diminished.

In conclusion, my best thanks are due to Professor Sidney Martin, F.R.S., for his kindness in giving me this work to do, and also in allowing me the use of his laboratory and apparatus.

7. PROTOCOL OF EXPERIMENTS.

I. *Experiments to Determine Symptoms, Fatal Dose, and* Post-Mortem *Lesions.*

Experiment 1.—Rabbit, weight 2125 grammes. Injection of 1/5 gramme of poison dissolved in 2 c.c. salt solution (=0·094 gramme per kilogramme). into the marginal vein of left ear. The solution was unfiltered. Almost immediately the animal began to open its mouth during inspiration, which was slow and laboured, the dyspnœa being inspiratory. The alæ nasi twitched. The animal tried to hop, but staggered and swayed. The limbs then became paralysed, the head dropped, the animal finally sank on its side and during a convulsion in which the body was stretched out rigidly it died. Death occurred in four minutes.

Post-mortem.—The heart was dilated. Both auricles and ventricles were full of clotted blood, on the right side black, on the left side bright red. The aorta also contained red blood clot. The portal vein contained a few dark blood clots, but the blood in it was mostly fluid. The venæ cavæ and jugular veins contained dark clot. The blood in the pulmonary veins was fluid.

Experiment 2.—Rabbit, weight 890 grammes. Intravenous injection of 1/10 gramme of filtered solution of poison (=0·112 gramme per kilogramme).

Immediately after the injection the animal commenced licking movements with the tongue and chewing movements. It pawed its mouth as if trying to remove something. Inspiratory dyspnœa was not such a marked feature as in the former case. Muscular weakness supervened and during a convulsion the animal died in three minutes after the injection. The hind legs were stretched out, the spine rigid and the head retracted.

Post-mortem immediately after death. The heart was dilated. No clots were found in any of the vessels. The blood on the left side of the heart was bright red, and on the right side dark in colour.

Experiment 3.—Rabbit, weight 1270 grammes. Intravenous injection of 1/5 gramme of the unfiltered solution (= 0·15 gramme per kilogramme). Chewing and licking movements began at once and then inspiratory dyspnœa, but this was not such a marked symptom as when smaller doses were used. The animal collapsed on its belly and a convulsion occurred, the head being retracted, the spine opisthotonic, and the hind legs extended. Death occurred in three minutes.

Post-mortem immediately after death. The changes were exactly the same as in the case of Experiment 1, and the blood clots were found in the same situations.

Experiment 4.—Rabbit, weight 1150 grammes. Intravenous injection of 1/12 gramme of the filtered solution (=0·072 gramme per kilogramme). In one minute the chewing and licking movements began and the animal threw its head backwards and forwards. Severe inspiratory dyspnœa occurred. General weakness supervened and after a convulsion death occured four minutes after injection of poison.

Post-mortem.—The heart had evidently stopped in diastole. No clots in any part of the vascular system were seen.

Experiment 5.—Rabbit, weight 1150 grammes. Intravenous injection of 3/40 gramme of filtered solution (= 0·065 gramme per kilogramme). The olution was *boiled* for half an hour and then allowed to cool before injection.

Death occurred in four minutes, the same symptoms occurring as described above. The final convulsion was practically absent.

Post-mortem.—The heart was dilated. No clots were found in any portion of the vascular system.

Experiment 6.—Rabbit, weight 1000 grammes. Intravenous injection of 1/20 gramme filtered solution (= 0·05 gramme per kilogramme). No symptoms occurred for five minutes and then the licking and chewing movements commenced, the animal appearing to try and remove some object from its mouth. Inspiratory dyspnœa occurred and finally muscular weakness. Immediately before death a convulsion occurred. Death took place 10 minutes after the injection.

Post-mortem.—The heart was in diastole. No clots were seen anywhere and the left side of the heart contained bright red blood as usual.

Experiment 7.—Rabbit, weight 1050 grammes. Intravenous injection of 1/30 gramme of the filtered solution (= 0·031 gramme per kilogramme). The symptoms began in exactly the same way as in all the previous rabbits. Inspiratory dyspnœa came on in an attack which lasted three minutes and was succeeded by a period of rapid shallow breathing of 160 per minute. In seven minutes an attack of inspiratory dyspnœa occurred which lasted a few minutes and this was again succeeded by a period of rapid breathing.

After one hour general weakness began to come on and the head drooped. The animal could hop and was not paralysed, but certainly weak. Respirations 160.

Two hours after the injection the animal was lying on its belly with the head thrown back and breathing rapidly. It could not hop, but rolled over on attempting to do so. It was apparently paralysed in the legs, but could still crawl on the belly.

The weakness became more profound and death occurred in two and a half hours after the injection, a slight convulsion, the whole body being stretched out and the head retracted, occurring just at death.

Post-mortem.—The heart was dilated and no clots were seen anywhere in the blood vessels. The blood in the left ventricle was bright red.

Experiment 8.—Rabbit, weight 1800 grammes. Subcutaneous injection of 1/20 gramme of the filtered solution (= 0·027 gramme per kilogramme). The animal developed no symptoms, and five days later it was quite normal.

On the fifth day after the injection, another injection of 1/20 gramme was given intravenously. Movements of the mouth and tongue occurred and slow inspiratory dyspnœa, the head being extended in inspiration and the mouth opened. In 10 minutes the inspiratory dyspnœa disappeared and the breathing became rapid.

The next day the animal seemed rather weak but otherwise normal. On this day another dose of 1/20 gramme was given intravenously. The same symptoms supervened and rapidly a general weakness appeared. Inspiratory dyspnœa was succeeded by rapid breathing and the animal died a quarter of an hour after the injection. Two spasms and fibrillary twitchings of the muscles occurred before death.

Post-mortem.—The heart was dilated, the cavity of the left ventricle being globular. The urine in the bladder contained albumen. The medulla and cervical and lumbar enlargements of the spinal cord were hardened, cut and stained by Nissl's method. No abnormal cells were to be seen.

Experiment 9.—Rabbit, weight 2125 grammes. Intravenous injection of 1/40 gramme of the filtered solution (= 0·011 gramme per kilogramme). In a quarter of an hour the animal was seized with an attack of inspiratory dyspnœa, but soon recovered from this and showed no further symptoms. The next day 1/16 gramme (= 0·029 gramme per kilogramme) was injected into a vein. In three minutes the movements of the mouth began and inspiratory dyspnœa also. Respiration, 30 per minute. Pulse 292 per minute. The heart sounds were normal and on auscultation of the bases of the lungs, air was heard to enter freely. Attacks of slow inspiratory dyspnœa alternated with attacks of rapid breathing. The animal died in two and a half hours after the injection.

Post-mortem.—Heart dilated. No other lesion.

Experiment 10.—Rabbit, weight 1350 grammes. Intravenous injection of 1/30 gramme of the filtered solution (= 0·024 gramme per kilogramme). The movements of the tongue and mouth began in one and a half minutes, and one minute later inspiratory dyspnœa commenced. Several attacks of inspiratory dyspnœa alternated with attacks of rapid breathing. No muscular weakness was to be seen. In three hours from the injection the animal had practically recovered. The next day 1/25 gramme (= 0·029 gramme per kilogramme) was injected intravenously. The same symptoms ensued and death occurred in 20 minutes after a few convulsive movements.

Post-mortem.—Heart dilated. No other lesion.

Experiment 11.—Rabbit, weight 1700 grammes. Intravenous injection of 1/30 gramme of the filtered solution (= 0·019 gramme per kilogramme). In three minutes inspiratory dyspnœa commenced. On auscultation air was found to enter the lungs all right. The heart was very irregular and 74 per minute in frequency. The irregularity seemed to affect both force and rhythm, the beats tended to occur in groups of threes and fives.

In about eight minutes the heart became regular, and 148 per minute in frequency; the respirations were 142 per minute, and the inspiratory dyspnœa ceased. After this the animal recovered. Three days later a second injection of 1/30 gramme was given. The same symptoms occurred, together with some muscular weakness.

The following day a third dose of 1/30 gramme was given. The symptoms were more severe than before. Half an hour after the injection the animal was lying collapsed and could not stand. Attacks of inspiratory dyspnœa occurred. The next day the animal had recovered, and a fourth injection of 1/30 gramme was given. The same symptoms occurred, and after a convulsion the animal died in 20 minutes.

Post-mortem.—The heart was dilated as in the other animals. The chest contained a little fluid on both sides, and there was œdema of the mediastinum. No clots could be found in the heart and vessels.

Experiment 12.—Cat, weight 2450 grammes. Intravenous injection of 1/5 gramme of the unfiltered solution (= 0·081 gramme per kilogramme). Very rapid breathing came on almost immediately, then the animal had a violent convulsion in which fæces were passed, and died at once (three minutes after the injection).

Post-mortem, immediately after death. The heart was distended with blood clot, which was bright red on the left side and extended into the aorta, and on the right side was dark in colour and extended into the venæ cavæ. There was no clot in the pulmonary vessels or portal vein.

Experiment 13.—Cat, weight 2120 grammes. Intravenous injection of 1/10 gramme of the filtered solution (= 0·047 gramme per kilogramme).

In two minutes after the injection the animal began to salivate, and licking and chewing movements commenced. No vomiting occurred, but a sort of retching and coughing, as if the animal were trying to remove some object from the throat. Inspiratory dyspnœa then commenced, and was succeeded by rapid breathing, the animal lying on its stomach with the head bent down. Then, after a violent convulsion, during which fæces were passed and the animal threw itself about, it died in six minutes after the injection.

Post-mortem.—The heart was dilated in both its cavities. No clotting of the blood in the heart or any of the vessels was seen.

Experiment 14.—Guinea-pig, weight 410 grammes. Intraperitoneal injection of 1/20 gramme (= 0·12 gramme per kilogramme). No symptoms appeared for about half an hour, and in one hour they were well marked. The animal lay on its belly, and when it attempted to run violent trembling came on and it staggered about. There was marked loss of power in the legs, especially the front ones, and the head sank down as if too heavy for the body. For some time the animal could run along, using chiefly the hind legs, but the weakness increased, and finally it could not move at all. If rolled on to one side it could hardly right itself. Finally it sank on to its side and, after a few gasps, died one and a half hours after the injection. The respirations were at first accelerated, but just before death they were slow. No convulsions or twitchings whatever occurred, and no inspiratory dyspnœa or chewing movements.

Post-mortem.—The heart was in diastole, and the left auricle in a state of fibrillary contractions. No clotting.

Experiment 15.—Guinea-pig, weight 410 grammes. Subcutaneous injection of 1/20 gramme of the poison (= 0·12 gramme per kilogramme). The symptoms began about the same time as those of the former pig. The respirations were accelerated, and there was marked shivering and trembling. The same weakness occurred, being most marked at first in the fore legs and head. After passing through a stage of almost complete paralysis the animal died one hour and ten minutes after the injection.

Post-mortem.—The heart went on beating with irregular and spasmodic contractions for ten minutes after death. No clotting.

II. *Blood-Pressure Experiments.*

In all the following blood-pressure experiments the poison was dissolved in salt solution, which was filtered or centrifugalised before injection. In the stimulation experiments the strength of the current was measured by the distance in centimetres of the secondary from the primary coil.

Poison Only.

Experiment 1.—Cat, weight 2610 grammes. Poison 1/8 gramme (= 0·047 gramme per kilogramme).

Blood Pressure.—The curve is naturally divided into two parts, corresponding to a sharp rise in the pressure with a succeeding fall, and a second long and slow rise to a maximum with a succeeding fall till death.

The pressure curve was unaltered for 12½ seconds after the injection, and the first rise then occurred. The pressure rose somewhat abruptly from 166 to 178 mm. Hg to 200 to 210 mm. Hg in 10 seconds, and during the next six seconds it fell to 184 mm. Hg. The second rise of pressure was more gradual, and attained its maximum point of 224 mm. Hg in the succeeding 73 seconds, the pressure during this time having risen 40 mm. Hg. From this point the curve gradually fell for 54 seconds, and then more rapidly for the last 38 seconds of life.

During the final fall there were three sudden descents of about 80 mm. Hg in the curve, obviously due to heart failure. The heart recovered itself after the first two falls, the pressure shooting up 60 and 40 mm. Hg respectively. The last fall was practically to the lowest point of the curve, and the heart only recovered itself by 10 mm. Hg before ceasing as the pressure fell to its lowest point of 20 mm. Hg above zero. It will be seen that the respiratory rhythm of the blood pressure becomes lost towards the end.

Heart Beats.—The rate of the heart was 213 per minute before injection. Until the pressure rose there was no alteration in the rate. During the first rise of pressure the heart beats became rather slower as the summit of the curve was reached; the number of beats during the 10 seconds of the first rise was 33, making a rate of 198 per minute. The beats also became rather larger. During the first fall of pressure, which lasted six seconds, 16 pulsations occurred, making a rate of 160 beats per minute, the pulsations also became larger.

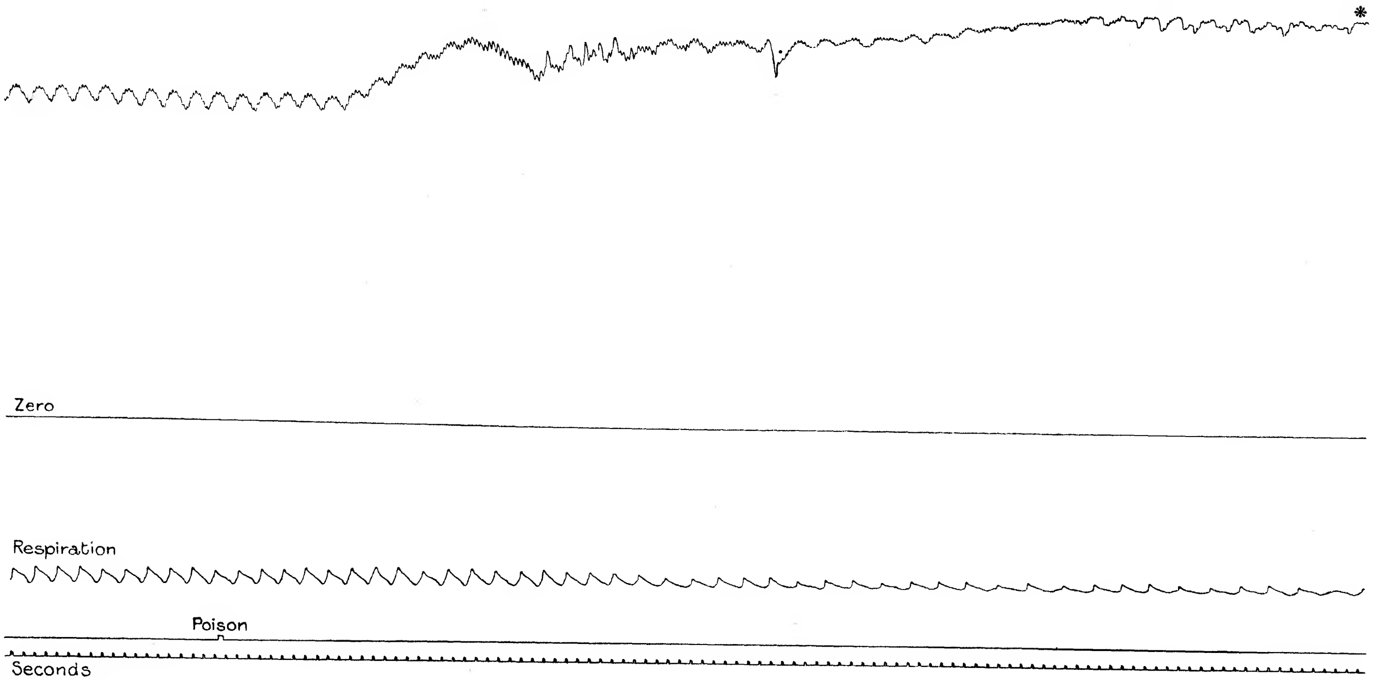
During the second rise of pressure the heart became gradually more and more rapid as the summit of the curve was reached, the rate at this point being 216 per minute. At the first part of the rise the pulsations were very irregular in size; towards the end they became much smaller as the rapidity increased, and they were also irregular. During the second and final fall of pressure the pulsations were very rapid and small, and towards the end were uncountable, the curve being practically a straight line.

Respirations.—The respiration was unaffected till the blood pressure fell to its lowest level, when five large inspirations were taken, inspiratory gasps following at intervals for the next 104 seconds, the blood-pressure curve meanwhile forming a straight line at about 20 mm. Hg above zero.

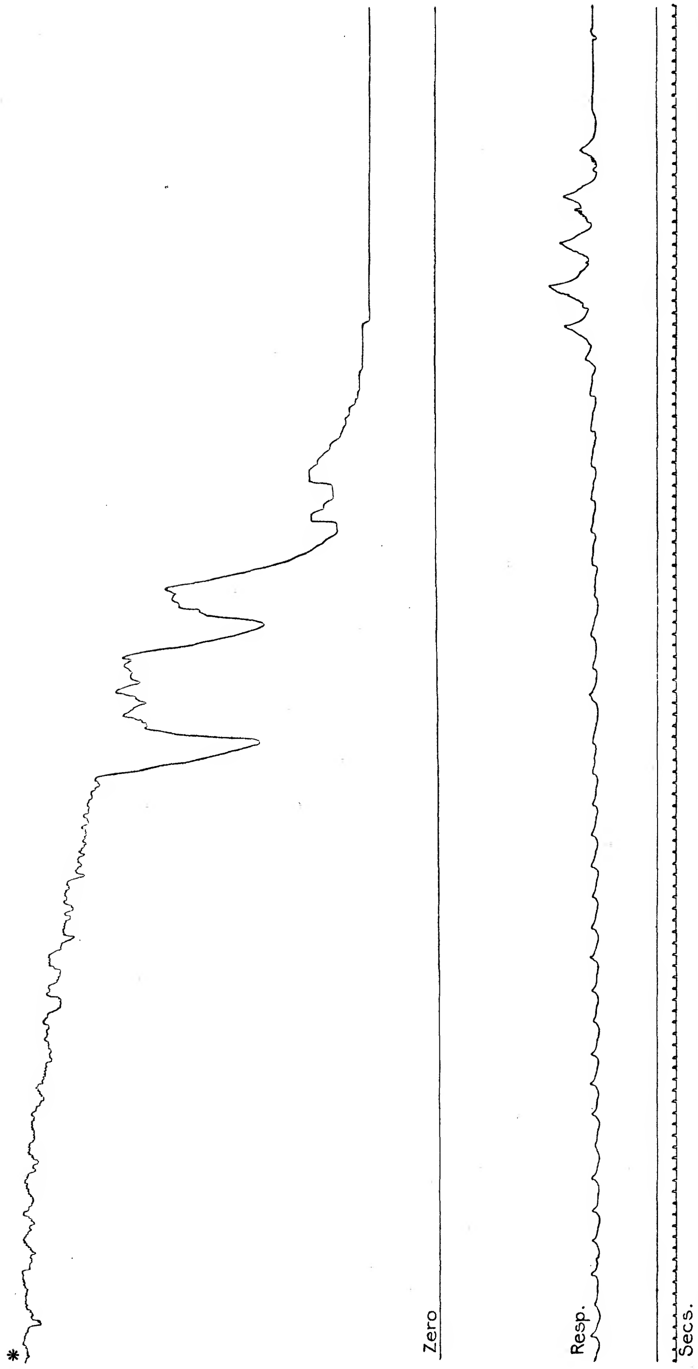
Experiment 2.—Cat, weight 1950 grammes. Poison 1/12 gramme (= 0·042 gramme per kilogramme).

Blood Pressure.—The first rise was very well marked, and commenced immediately the injection was given, and the subsequent fall also, but the second rise was not seen, the pressure, after maintaining itself for a little while, gradually dropping to its lowest point.

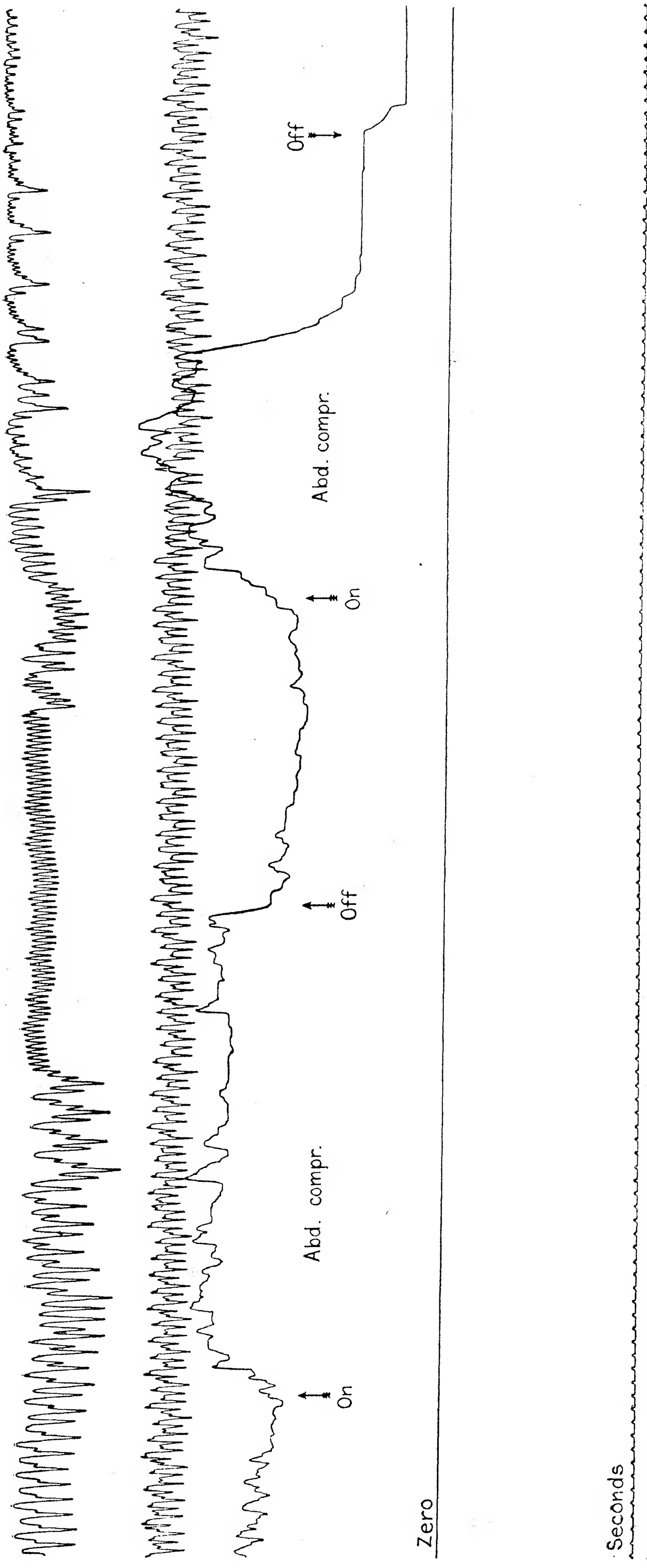
The pressure before injection was 120 to 126 mm. Hg, and the first rise reached its maximum point of 178 to 184 mm. Hg in 40 seconds. It was 154 to 164 mm. Hg 80 seconds later, and from this point it fell gradually to its lowest point of 20 mm. Hg above the zero line. There were no sudden falls of pressure as the curve was descending. The second rise in pressure, as I have already mentioned, is due to some extent to the heart, and it did not occur in this case, probably because that organ was unable to maintain the pressure. The cat was not a strong animal, and it breathed somewhat irregularly the whole time. The respiratory rhythm of the pressure curve becomes lost towards the end.



Experiment 1.—This tracing shows the effects of injection of the poison alone. The point of injection of the poison is marked on the line immediately above the tracing of the time, which is marked in seconds. An initial rise of blood pressure is seen followed by



a slight fall associated with a slower rate and increased size of the heart beats. The pressure then slowly rises to a maximum and falls till death occurs. The respiration stopped after the heart, and gasps were taken for 104 seconds subsequently.



EXPERIMENT 3.—This tracing illustrates the effect of abdominal compression as the blood pressure is falling. The drum had gone round three times, and when the abdomen was compressed the blood pressure was reaching its lowest point. On the second occasion it is seen that the heart suddenly failed during the compression.

Heart Beats.—At the end of the first rise of pressure the heart became a little slower and the beats slightly larger. At the end of the first fall the rate of the pulsations had dropped from 195 per minute to 126 per minute, and were decidedly larger. After this point till death the pulsations became gradually smaller and the rate more frequent, the latter being 246 when they could be last counted, about 100 seconds before the pressure reached its lowest point.

Respiration.—Before the injection was given the respirations were a little irregular, and they were quite unaltered by the injection. They became a trifle shallow during the last minute of life. As the heart stopped about 10 small irregular respirations occurred, and a minute later three small inspiratory gasps at intervals of 10 seconds were taken.

Compression of Abdomen.

Experiment 3.—Cat, weight 3220 grammes. Poison 1/10 gramme (= 0·031 gramme per kilogramme). A smaller dose of the poison was given so as to produce a slow heart failure. The animal lived for about half an hour. The kymograph drum was allowed to go round twice, and it had commenced its third revolution when the blood pressure, which had been gradually falling, reached 60 mm. Hg. The abdomen was compressed, and the blood pressure immediately went up to 95 mm. Hg; the compression was kept up for 37 seconds, and as soon as it was relaxed the blood pressure immediately fell to 60 mm. Hg again.

The abdomen was again compressed for 35 seconds. The blood pressure rose to a maximum of 120 mm. Hg, and when the compression had been maintained for 18 seconds the blood pressure suddenly fell straight down to 34 mm. Hg and the heart stopped. When the compression was relaxed there was a further fall to 20 mm. Hg above zero. The heart had failed before the extra work that was presented to it by increasing the flow of blood into its right cavities during diastole.

Section and Excitation of the Vagi.

Experiment 4.—Cat, weight 2750 grammes. Both vagi divided before injection. Poison 1/10 gramme (= 0·036 gramme per kilogramme), the dose being repeated.

Blood Pressure.—Immediately the injection had been given the blood pressure began to rise, and during the first six minutes after the injection it rose from 162 to 180 mm. Hg to a maximum of 194 to 210 mm. Hg. After this it gradually fell to 184 to 162 mm. Hg, and now a second injection of 1/10 gramme of the poison was administered. After the second injection the pressure rose to 169 to 170 mm. Hg in 33 seconds and then fell rapidly to 30 mm. Hg above zero owing to heart failure.

This pressure curve cannot be divided into two parts as described above when the vagi are intact. The pressure gradually rose in a long single curve to its highest point, and from this point it gradually fell.

Respiration.—The respirations were not affected till the blood pressure finally fell, except that they became slightly shallower. Large inspiratory gasps were taken for three minutes after the blood pressure had fallen to its lowest limit.

Experiment 5.—Cat, weight 3220 grammes. Both vagi divided before injection. Poison 1/10 gramme (= 0·034 gramme per kilogramme).

Blood Pressure.—The blood pressure began to rise six seconds after the injection of the poison, and attained its maximum height of 216 mm. Hg in 86 seconds, having risen from 174 mm. Hg. After this there was a steady fall till the heart stopped in 146 seconds.

Heart Beats.—Immediately before injection the rate of the heart was 258 per minute, and when the blood pressure had risen to its maximum point the rate was unaltered. Before the final fall it had increased to 261 per minute. There was no fall in the blood pressure during the early stage of poisoning, and the pulse rate did not notably increase towards the end of life.

Respirations.—The respirations were not affected until the blood pressure fell, when they became irregular as the heart stopped, inspiratory gasps continuing at intervals for about three minutes after the blood pressure had reached its lowest point.

Excitation of Vagus.—The left vagus was stimulated, the strength of current being 10 (secondary coil at 10 cm. distance). The stimulation was continued for 10 seconds. Before stimulation the blood pressure was 216 mm. Hg, and at the end of stimulation it was 210 mm. Hg; for the next six seconds it gradually fell to 190 mm. Hg, and then rose almost to its former height (210 mm. Hg). The rate of the heart fell by about eight beats per minute.

The vagus was again stimulated 50 seconds later, the strength of the current being increased to six and the time to 12 seconds. This time there was no obvious effect produced upon the blood pressure. Before the poison was administered a stimulus of strength 12 applied to the left vagus produced an immediate fall in the blood pressure of over 30 mm. Hg.

Experiment 6.—Cat, weight 2720 grammes. Right vagus divided before injection. Poison 1/15 gramme (= 0·024 gramme per kilogramme).

Blood Pressure.—The pressure curve began to rise 13 seconds after the commencement of the injection, and in 26 seconds it had risen from 160 mm. Hg to 182 mm. Hg. There then occurred a slight fall in the pressure to 178 mm. Hg. After 220 seconds the pressure had risen to 200 mm. Hg, its maximum point, and then succeeded a rapid fall to 20 mm. Hg as the animal died.

Pulse Rate.—Before the injection the rate of the heart was 228 per minute after the preliminary rise of pressure, and when it was falling the rate fell to 204 per minute. It again increased, and 120 seconds after the injection, which was the last point at which it could be counted, it had reached 240 per minute.

Respiration.—The respiration was unaffected and became spasmodic as the heart stopped. After the blood pressure had fallen to its lowest point a series of very deep inspiratory gasps occurred, which gradually died away in four minutes.

Stimulation of the Right Vagus.—Before the poison was administered stimulation of the vagus (strength 12) produced a fall in the blood pressure of over 30 mm. Hg. The vagus was stimulated 93 seconds after the injection was given (strength 12) for 15 seconds. After the stimulation had ceased a hardly appreciable fall in the blood pressure occurred. The vagus was stimulated 40 seconds later (strength 10) for 17 seconds, and during the stimulation the pressure rose somewhat higher. When the pressure had commenced to fall rapidly, a third stimulation for five seconds (strength 10) produced no effect on the pressure curve.

Experiment 7.—Cat, weight 2500 grammes. Poison 1/15 gramme (= 0·026 gramme per kilogramme).

Blood Pressure.—Ninety seconds after the injection the blood pressure had risen from 184 mm. Hg to 216 mm. Hg. The right vagus was now cut and the pressure at once went up, reaching a height of 226 mm. Hg in one second. The pressure gradually went up to 232 mm. Hg during the 102 seconds following, and now the left vagus was cut, but no alteration occurred in the pressure curve except that the respiratory undulations became well marked. The pressure fell to its lowest point 180 seconds later.

Heart Beats.—When the right vagus was cut the heart was accelerated in rate by 24 beats per minute. No notable acceleration occurred after the left vagus was cut, but the heart beats gradually increased in frequency and just before the blood pressure finally fell they were 246 per minute.

Respirations.—The respirations were markedly affected on division of the vagi, becoming quite characteristic in type.

Experiment 8.—Cat, weight 2920 grammes. Poison 1/10 gramme (= 0·034 gramme per kilogramme).

Blood Pressure.—The blood pressure started to rise 20 seconds after the injection, and went up from 170 mm. Hg to 194 mm. Hg. Then followed the usual slight fall to 184 mm. Hg, and later a steady rise to a maximum of 224 mm. Hg 120 seconds after the injection. From this point the pressure steadily fell during the next 100 seconds to 30 mm. Hg. As the blood pressure was declining (200 seconds after injection) the left vagus was cut, but this procedure brought about no effect whatever upon the blood pressure. The right vagus was cut 10 seconds later with a similar result.

Respirations.—Although there was no effect upon the blood pressure, yet after both vagi had been divided typical vagus respiration ensued. Inspiratory gasps were taken for five minutes after the blood pressure had reached its lowest point.

Heart Beats.—Before injection the frequency of the heart beats was 168 per minute. Just before the final fall it was 270 per minute.

Experiment 9.—Cat, weight 2130 grammes. Poison 1/20 gramme (= 0·023 gramme per kilogramme).

Blood Pressure.—The injection of the poison occupied 15 seconds, and the blood pressure began to rise at the end of the eighth second. At the end of 20 seconds the pressure had risen from 136 to 140 mm. Hg to 166 to 168 mm. Hg. During the next 25 seconds several sudden falls of from 10 to 16 mm. Hg occurred. The pressure then became steady and commenced to rise slowly.

The right vagus was cut at this moment (54 seconds after the injection) and 19 seconds later the left vagus was cut. These sections produced no alteration in the steady rise of blood pressure, except such as were due to the altered respiratory rhythm.

The pressure reached its maximum point of 194 to 196 mm. Hg 131 seconds after the injection; it then commenced falling very rapidly, and reached 40 mm. Hg above zero in 40 seconds (three minutes after the injection).

Heart Beats.—During the first rise of blood pressure the pulse rate remained at 180 per second, the same as it was before the injection. During the next period of the curve, when the falls in pressure were taking place, the rate of the heart sank to 156 per minute. Later it became accelerated again (about 228 per minute). The two sections did not materially interfere with the frequency, which gradually increased up to 249 per minute when the blood pressure reached its height. It maintained this rate as the pressure commenced to fall. The beats had now become extremely small.

Respiration.—No change occurred in the respirations until the second vagus had been cut, and then the respirations became of the vagus type. The respirations became irregular and small as the heart stopped, and inspiratory gasps were taken at intervals for 100 seconds later.

Stimulation of Vagus.—Stimulation of the vagus 26 seconds after the second vagus had been divided produced no effect whatever upon the heart beats or blood pressure. No alteration was produced on again stimulating the nerve with the full strength of current when the blood pressure had attained its maximum point. A marked effect was, however, produced upon respiration, which stopped suddenly. A third stimulation with the full strength of current for a period of seven seconds was applied when the blood pressure had commenced falling, but no effect whatever was produced on the blood pressure or heart beats although the respiration stopped.

Experiment 10.—Cat, weight 2930 grammes, poison 1/20 gramme (= 0·017 gramme per kilogramme).

Blood Pressure.—The blood pressure began to rise at once, and from 132 to 146 mm. Hg it reached 164 to 174 mm. Hg in 32 seconds. After remaining stationary for 35 seconds it began to fall. When the pressure had fallen to 150 to 168 mm. Hg the left vagus was cut, with the result that the pressure immediately rose, and in 15 seconds reached 180 to 192 mm. Hg. A second fall now occurred to 166 to 174 mm. Hg, and finally the pressure rose again in a long curve to a maximum of 208 to 218 mm. Hg, and from this point it gradually fell till death. Section of the right vagus before the maximum point was reached produced no alteration in the pressure curve. The blood-pressure curve fell very gradually and had many irregular rises and falls on it towards the end. It reached 24 mm. Hg in 17½ minutes after the poison was injected, and at this point death occurred.

Heart Beats.—During the first rise the rate of heart beats was unaltered. Whilst the pressure was stationary and during the first fall the rate was slowed from 231 to 216 per minute. After section of the left vagus the rapidity slightly increased to 220 per minute, and during the second fall the rapidity was 214 per minute.

From this point the rapidity gradually increased to 255 per minute when the blood pressure was at its height. When the pressure was finally falling, 100 seconds later, the rapidity was still 255 per minute, and after this the pulsations were too small to count.

Respiration.—The respirations were very irregular during the whole time, and typical vagus respiration occurred after section of both vagi.

Inspiratory gasps continued for from two to three minutes after the heart had stopped.

Stimulation of the Vagi.—The vagi were stimulated 10 times, commencing just when the blood-pressure curve was starting on its rise to the maximum point and ending about two minutes before the heart stopped. On each occasion there was no effect whatever upon the blood-pressure curve or upon the heart beats.

Experiment 11.—Rabbit, weight 2210 grammes, poison 1/20 gramme (= 0·022 gramme per kilogramme). Both the vagi were divided before the poison was injected.

Blood Pressure.—The blood pressure rose from 124 to 130 mm. Hg to a maximum height of 168 to 170 mm. Hg during the 39 seconds after the poison was injected. Death occurred 84 seconds later.

Stimulation of Vagus.—The left vagus was stimulated (strength 10) just as the pressure curve reached its maximum height, but no effect was produced on the blood pressure. The vagus was again stimulated as the blood pressure was falling, but there was produced no effect upon the curve.

Experiment 12.—Rabbit, weight 3065 grammes, poison 1/5 gramme (= 0·065 gramme per kilogramme). Both vagi divided before injection.

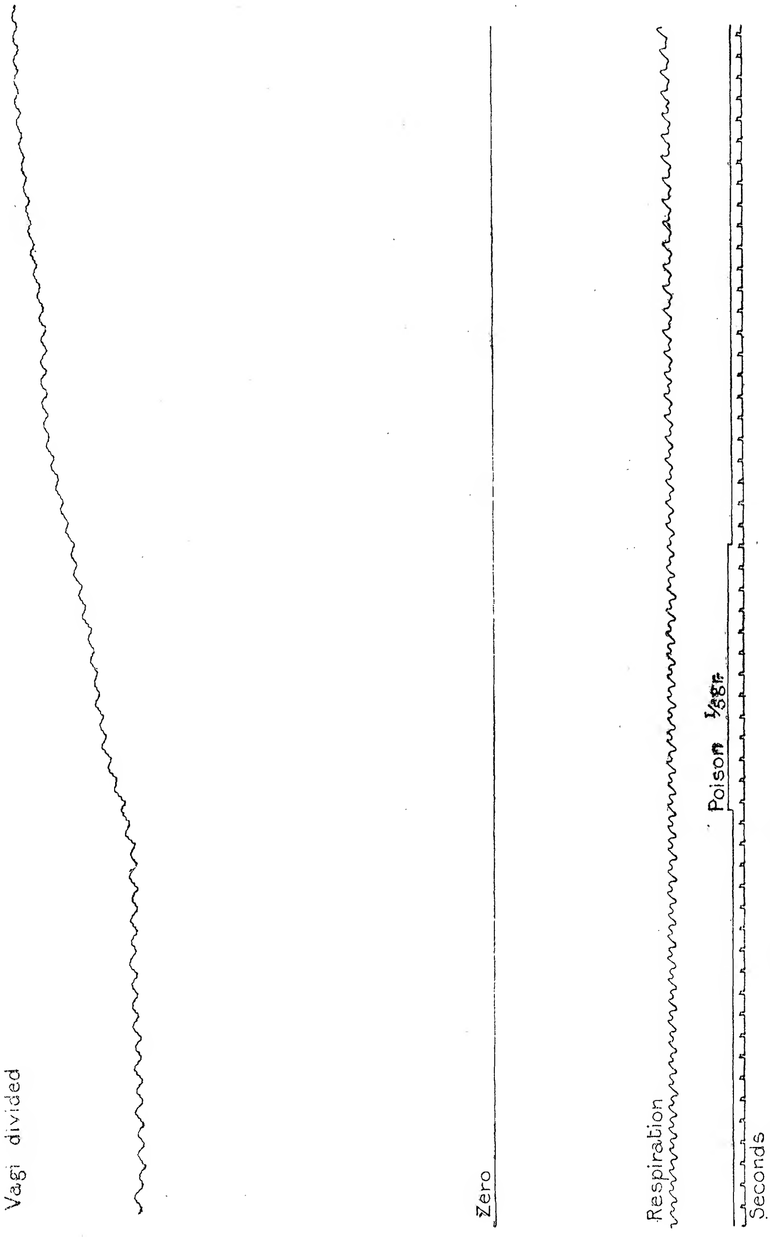
Blood Pressure.—The pressure immediately began to rise, and from 144 to 146 mm. Hg it rose to a maximum of 190 to 192 mm. Hg during the 27 seconds after the injection. This maximum height was maintained for 15 seconds, when the pressure commenced falling, and death occurred one and a half minutes after the poison was injected.

Stimulation of Vagus.—The left vagus was stimulated (strength 10) when the blood pressure had attained its maximum height. There was no direct effect upon the blood-pressure curve, but it was altered indirectly through the effect of the stimulation upon respiration. A second stimulation produced no result upon the blood pressure, although respiration was affected as before.

Section of Spinal Cord.

Experiment 13.—Cat, weight 2720 grammes. The spinal cord was divided at the level of the third cervical nerve. Artificial respiration was maintained at a rate of 39 per minute. Poison 1/20 gramme injected intravenously (= 0·018 gramme per kilogramme).

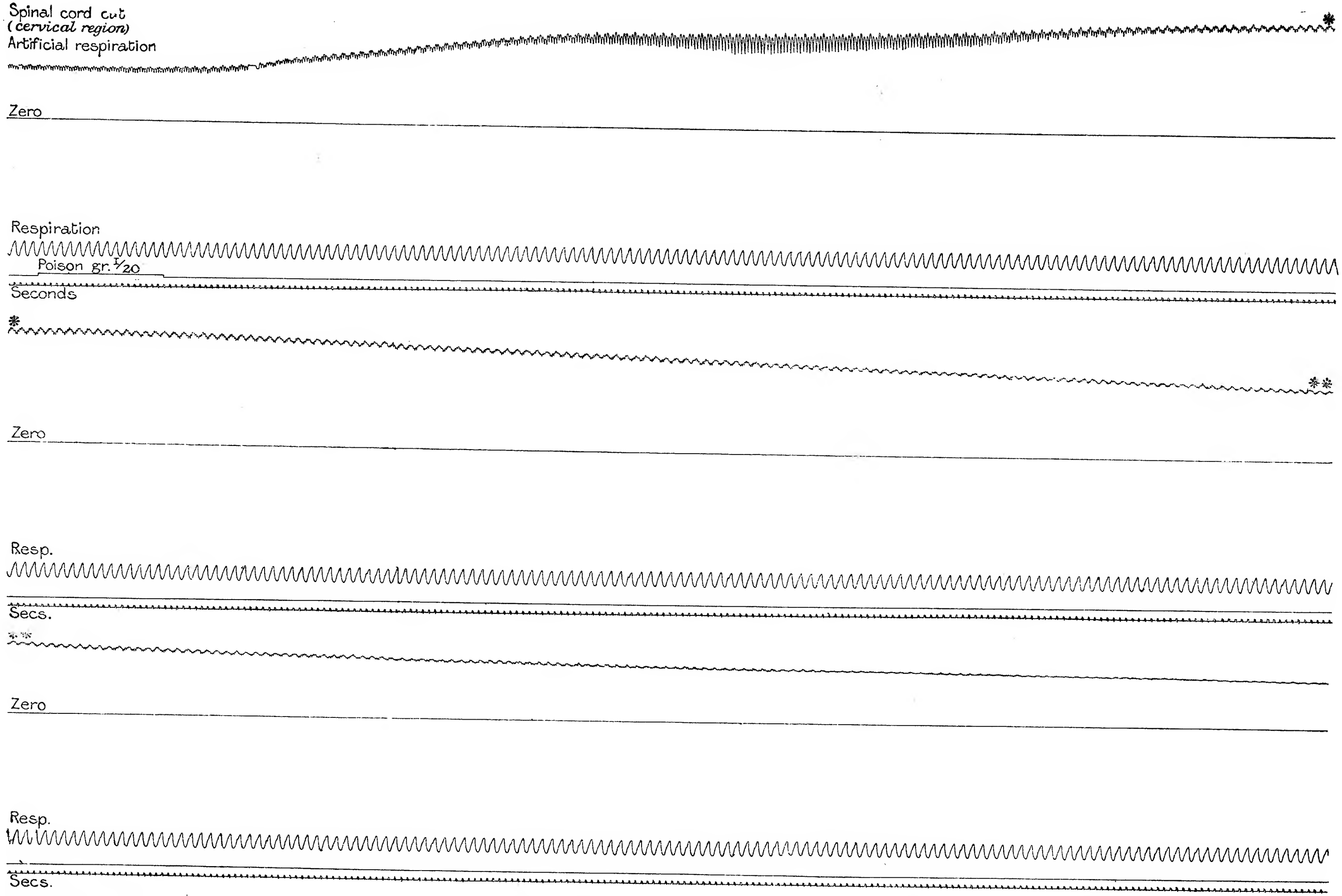
Blood Pressure.—The rise in pressure commenced 15 seconds after the injection was given, and from a height of 38 to 40 mm. Hg it attained a maximum height of 80 to 84 mm. Hg 200 seconds after the injection was given. From this point the pressure curve gradually fell till the heart stopped about seven minutes later. Before the pressure curve attained its



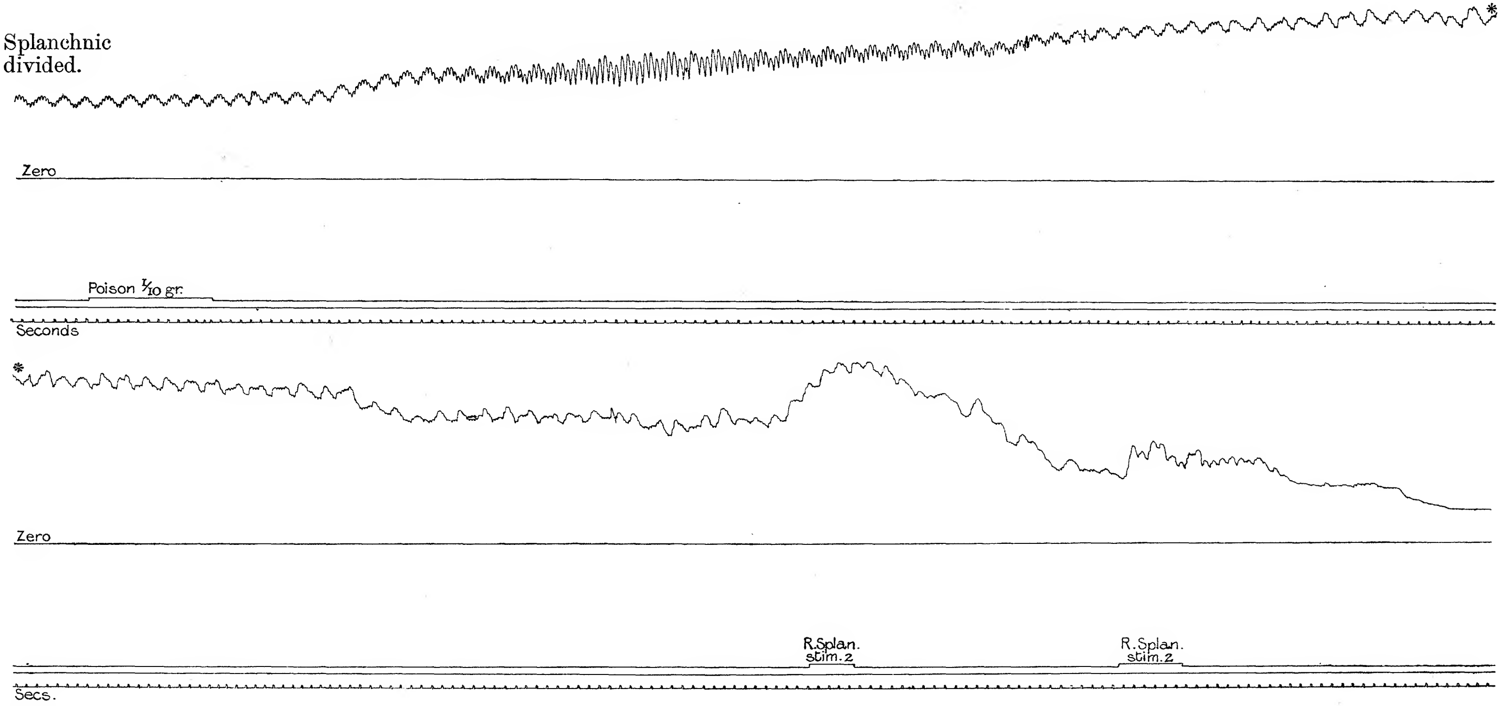
EXPERIMENT 12.—This tracing shows that the blood pressure still rises on injection of the poison after both vagi have been divided. It also shows that the slight fall, with slowing of the pulse, which occurs after the initial rise of blood pressure, does not occur when the vagi are divided.

maximum point it was interrupted by a very slight fall with slowing of the heart and increased size of the beats.

Heart Beats.—Before the injection was given the rate of the heart beats was 153 per minute. During the period of large heart beats the rate was 114 per minute, the size of the variations in pressure being 12 mm. Hg.



EXPERIMENT 13.—The spinal cord was cut previous to the injection of the poison in this experiment, and it is seen that, notwithstanding the section, the blood pressure rises and falls in the same manner as it does when the vasomotor system is intact.



Experiment 15.—The effect of injection of the poison after the splanchnic nerves have been divided is seen here. The blood pressure rises in a long curve as when these nerves are intact. The right splanchnic was stimulated twice as the pressure was falling, with a resulting rise in the pressure on each occasion, although only slight in the second case, as the heart was almost dead.

When the pressure curve was at its maximum height the rate was 204 per minute. The beats became much smaller and 228 in frequency as the pressure was falling. The last time the beats could be distinguished the rate was 280 per minute.

Experiment 14.—Cat, weight 2750 grammes. Spinal cord cut opposite third cervical nerve. Poison 1/20 gramme given twice (= 0·018 gramme per kilogramme).

The same sequence of events was observed as in Experiment 13. After a second injection of the same amount of poison during the period of large heart beats the pressure rose somewhat suddenly, the heart beats becoming smaller and showing a respiratory rhythm. Towards death the heart beats became irregular and rapid.

Section of Splanchnic Nerves.

Experiment 15.—Cat, weight 2470 grammes. Artificial respiration. The chest was opened on both sides, and both splanchnic nerves divided above the diaphragm. Poison 1/10 gramme injected (= 0·04 gramme per kilogramme).

Blood Pressure.—The blood pressure commenced rising 12 seconds after the injection was given. During the rise a period of slowing of the heart beats occurred as in the spinal cord experiments. This only lasted about 25 seconds, and slightly interrupted the rise of blood pressure. The maximum height of the blood pressure was 126 to 138 mm. Hg, and this occurred two minutes after injection, the blood pressure before injection being 56 to 64 mm. Hg. During the next 70 seconds the pressure gradually fell to 90 to 100 mm. Hg. The right splanchnic nerve was now stimulated (strength of current, 12), and the pressure in response to this immediately commenced rising and reached the height of 136 to 144 mm. Hg. In the next 25 seconds it gradually fell to 50 mm. Hg. The splanchnic nerve was again stimulated with the same strength of current, and the blood pressure rose to 80 mm. Hg. The heart now rapidly failed, and in 20 seconds had stopped, the pressure falling to 20 mm. Hg above zero.

Before injection the rate of the heart was 198 per minute. As the pressure was rising the rate fell to 117 per minute. When the maximum pressure was reached the frequency was 249 per minute. As the pressure fell the heart began beating irregularly and the rate was 255 per minute.

Previous Injection of Apocodein.

Experiment 16.—Rabbit, weight 2720 grammes. Apocodein 1/10 gramme injected (= 0·036 gramme per kilogramme). The blood pressure immediately fell from 84 to 50 mm. Hg. Stimulation of the sciatic nerve now produced no rise of blood pressure, showing that the peripheral terminations of the vasomotor nerves were paralysed. Poison 1/10 gramme (= 0·036 gramme per kilogramme) was now injected. The blood pressure went up to a maximum height of 120 mm. Hg and from this point the pressure fell as in all the other animals as the heart failed.

Experiment 17.—Rabbit, weight 2380 grammes. Both vagi divided. Blood pressure 124 mm. Hg. Apocodein 1/10 gramme injected (= 0·042 gramme per kilogramme). The blood pressure after a slight rise rapidly fell to 84 mm. Hg. Stimulation of the sciatic nerve produced a slight rise of 4 mm. Hg and therefore a second injection of the same dose of apocodein was administered. After this, stimulation of the sciatic nerve produced no rise in the blood pressure, which remained at 84 mm. Hg.

Poison 1/10 gramme (= 0·042 gramme per kilogramme) was now injected. At the end of the injection the blood pressure commenced to rise steadily to a maximum of 160 mm. Hg. From this point the pressure fell in the usual way, the action of the heart being irregular. The sciatic nerve was stimulated four times after the poison was injected and the slight alterations occurring in the blood-pressure curve are secondary to the alterations in the respirations.

Stimulation of the Depressor Nerve.

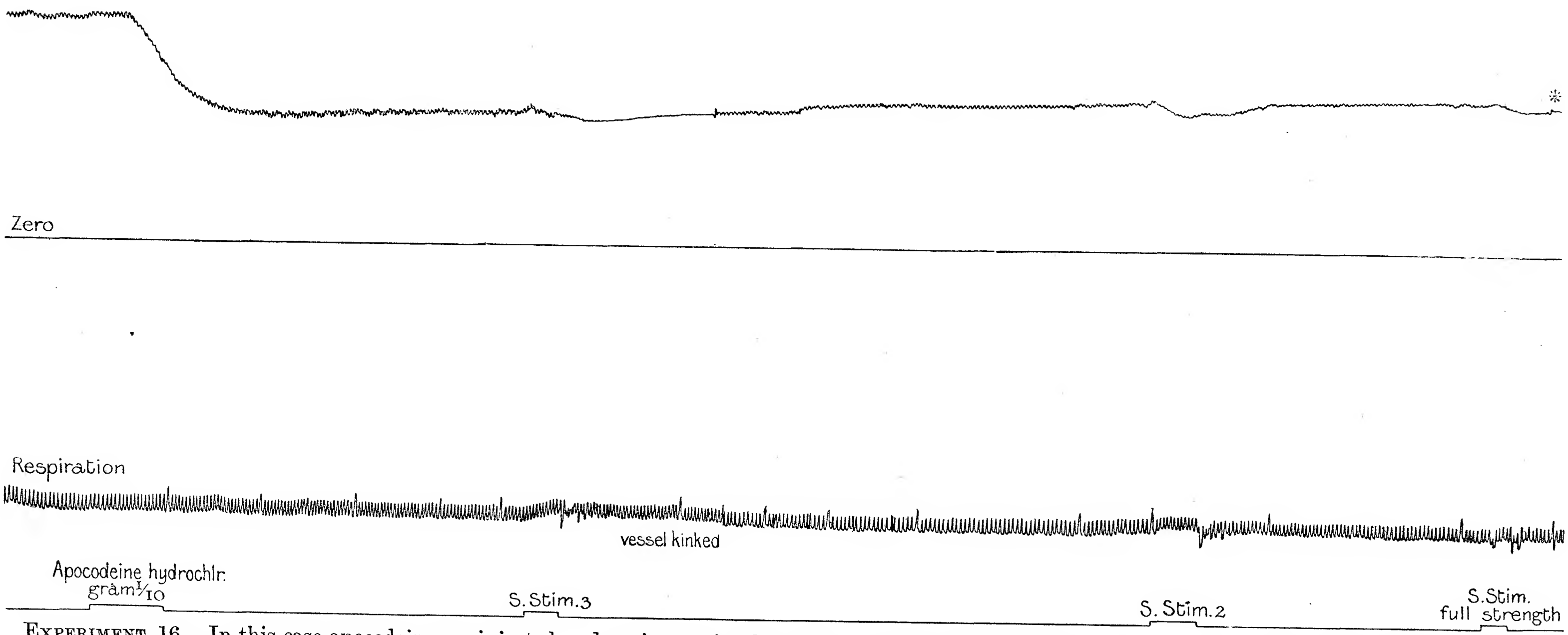
Experiment 18.—Rabbit, weight 2650 grammes. Left depressor nerve cut. Poison 1/30 gramme was injected intravenously (= 0·012 gramme per kilogramme).

Blood pressure.—After the pressure had risen in the usual way as the result of the injection, the central end of the depressor nerve was stimulated three times, the last stimulation being applied five minutes after the poison was injected. On each occasion the blood pressure fell to the same extent as it did on stimulation of the depressor before the poison was injected.

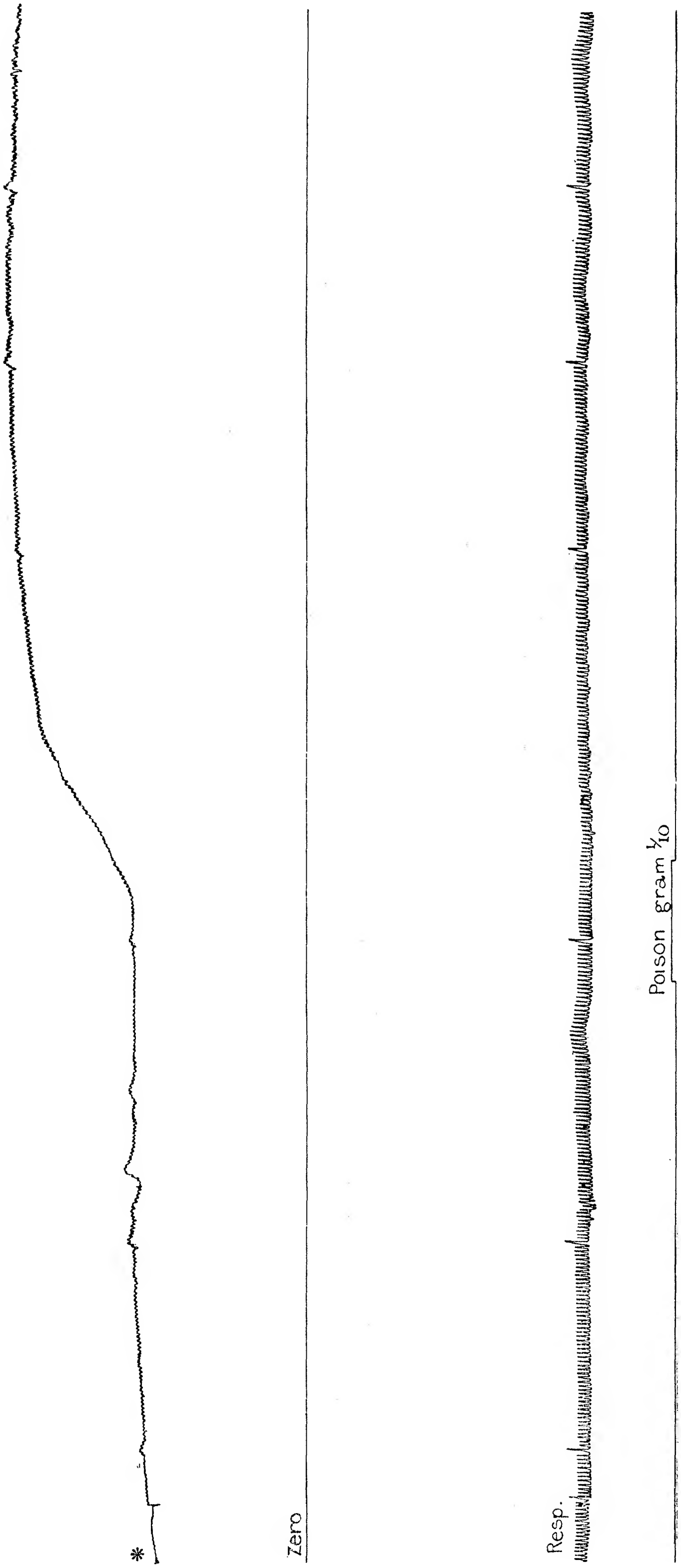
A second injection of poison (1/30 gramme) was administered six minutes after the first. After the blood pressure had risen as the result of the injection the depressor was stimulated five times.

The last stimulation was applied six minutes after the second injection. On each occasion except the first, when the stimulation was applied just as the blood pressure was commencing to rise as a result of the injection of the poison, the fall of pressure was practically to the same degree.

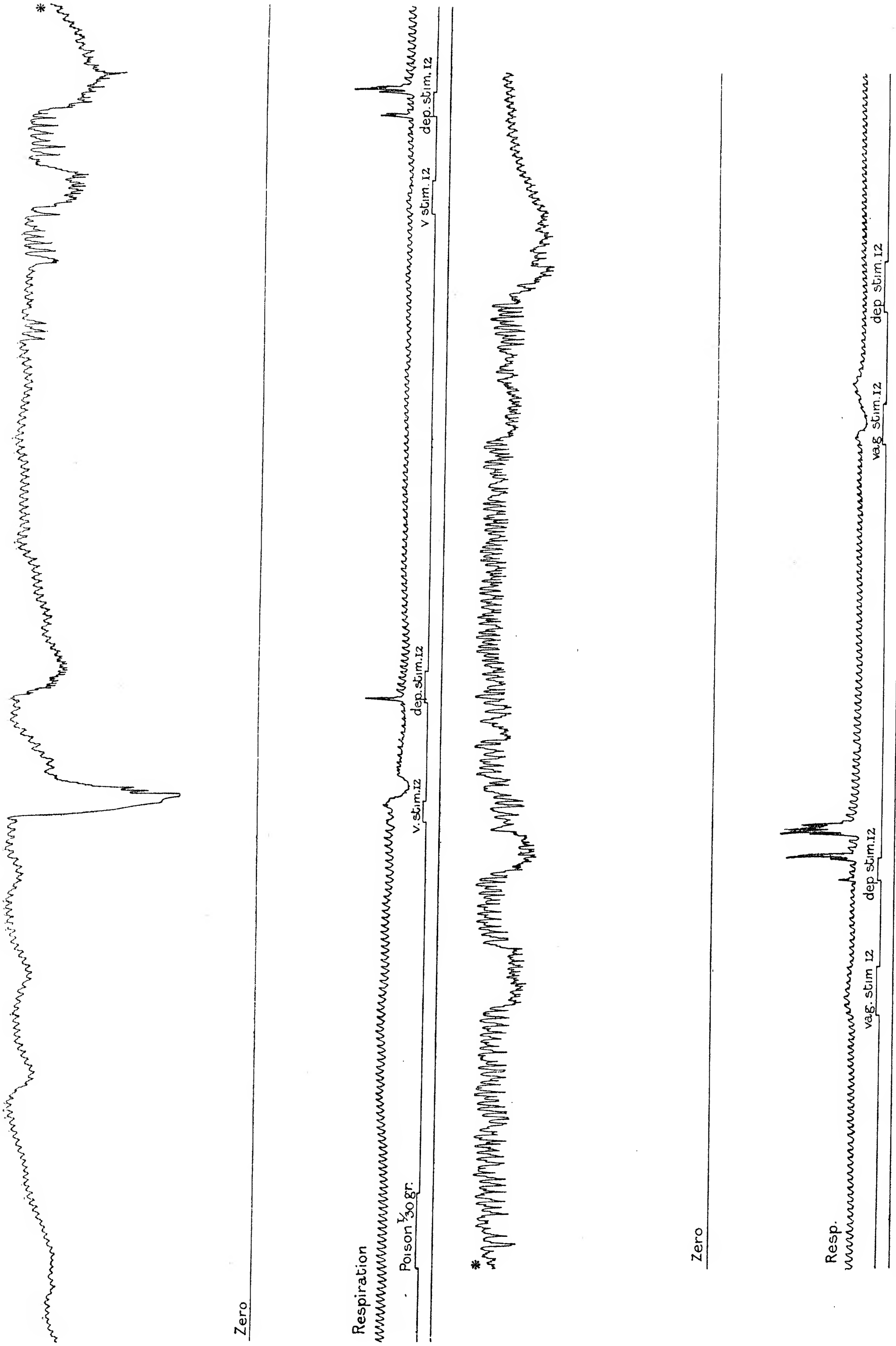
When the last two stimuli were applied the blood pressure had commenced to fall and the heart to beat irregularly. A third injection of poison (1/30 gramme) was given before the blood pressure had reached



Experiment 16.—In this case apocodein was injected and, as is seen in the tracing, produced a fall in the blood pressure. Stimulation of the central end of the divided sciatic nerve now produced no reflex effect upon the blood pressure. On injection of the poison, however, the blood pressure went up in the usual manner.



Experiment 16—*continued.*



EXPERIMENT 19.—This tracing shows the effect of four excitations of the vagus, the depressor nerve being stimulated immediately after the vagus on each occasion. The same strength of current was used for each stimulation. The effect of the vagus stimulation becomes rapidly less, but that of the depressor remains practically the same. If a larger dose of poison is used the vagus ceases to respond much earlier.

its lowest point and no rise of pressure resulted. Stimulation of the depressor three times still caused a fall in the pressure even at this late stage. The falls, however, were less marked than the former ones.

Experiment 19.—Rabbit, weight 2400 grammes. Left vagus cut. Poison 1/30 gramme injected intravenously (= 0·013 gramme per kilogramme).

Blood pressure.—After the pressure had risen the vagus was stimulated at quite an early stage (strength 12). The pressure at once fell from 136 mm. Hg to 40 mm. Hg. The depressor was stimulated immediately afterwards (strength 12) and the pressure fell from 132 to 136 mm. Hg to 104 to 108 mm. Hg. The vagus, and immediately afterwards the depressor were stimulated three times subsequently with the same strength of current. The vagus effect became each time less marked, on the third occasion the pressure only falling 10 mm. Hg. The depressor effect, however, remained the same till the end.

A second injection of poison was administered and stimulation of the vagus on three occasions produced no effect whatever, although the strength of the current was increased. Stimulation of the depressor, however produced a fall in the blood pressure of 20 mm. Hg just before the animal died.

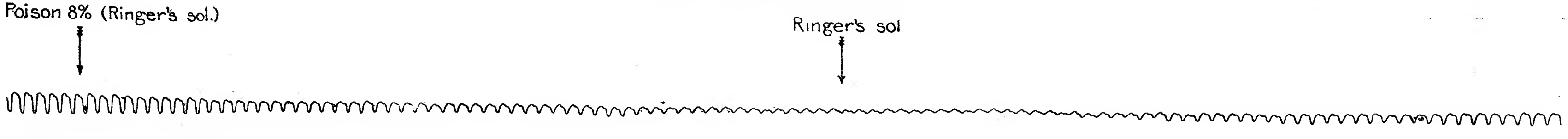
III. *Frog Heart Experiments.*

Experiment 1. *Pithed frog.*—The poison was dissolved in Ringer's solution (1/15 gramme to 1 c.c.) and the heart kept moist by occasionally applying the solution with a brush. The rate of the heart beats before the application was 42 per minute. During the application the rate finally sank to 30 per minute, the force of the ventricular systole being much weaker than that of the auricle. The ventricle occasionally took on an independent rhythm and its beats gradually became weaker and weaker till it finally stopped in diastole, the auricle continuing to beat after the ventricle had stopped. The auricle finally stopped and washing with Ringer's solution failed to restore the heart.

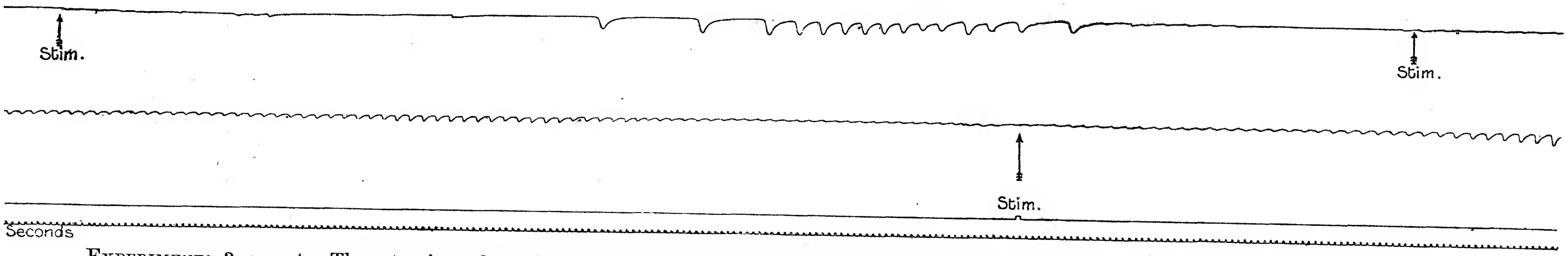
Experiment 2. *Pithed frog.*—Poison 8 per cent in Ringer's solution. When the heart had almost stopped the poison was washed off with Ringer's solution and the heart kept constantly moist with it. The heart finally recommenced to beat in the normal manner.

Experiment 3. *Pithed Frog.*—Poison 1/5 gramme to 1 c.c. salt solution. The contractions of the ventricle gradually became smaller and smaller, the rate declining from 42 to 36 per minute, and it finally stopped in diastole. Whilst the auricle was still contracting the sinus was stimulated with an induced current. Complete standstill resulted for about 25 seconds and then

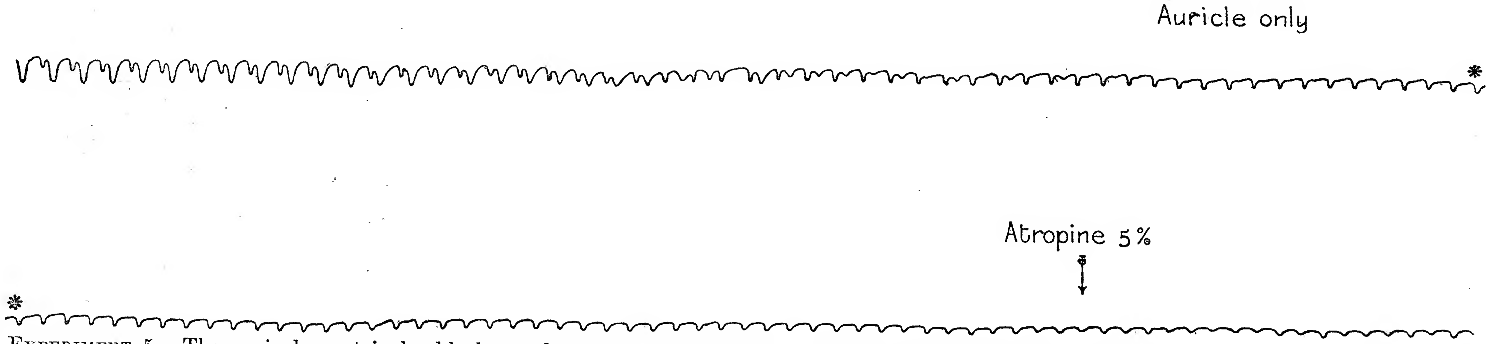
FROG HEART EXPERIMENTS.



EXPERIMENT 2.—This tracing shows the gradual stoppage of the frog's heart under the influence of the poison, and its revival by washing with Ringer's solution when the ventricle has almost stopped.

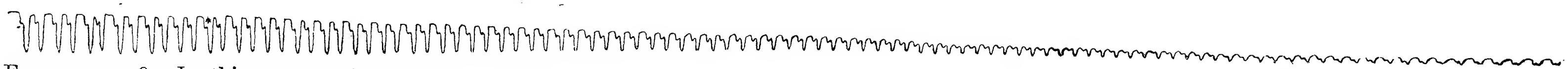


EXPERIMENTS 3 AND 4.—These tracings show that the heart may be temporarily revived by the application of an electrical stimulus to the sinus.



EXPERIMENT 5.—The auriculo-ventricular block can be seen in this tracing. Some of the auricular waves fail to pass over to the ventricle. The ventricle finally stops and the auricle goes on beating. Application of atropine fails to produce any effect and the auricle stops in diastole.

Atropine 5 %.
Poison 8 % 70 seconds later.



EXPERIMENT 6.—In this case atropine was first applied to the heart, and subsequently a solution of the poison brought the heart to a diastolic standstill in spite of the action of the atropine.

the heart commenced beating again, the beats gradually increasing until they reached their former size. The rate was 27 per minute.

On the application of more of the poisoned solution, the heart again stopped. A second stimulation after a longer latent period than before caused the heart to recommence beating. This time the beats did not attain their former size. Rate, 21 per minute, the beats being somewhat irregular. The heart soon stopped on its own accord, and a third stimulation restarted the contractions, which gradually died away, and now a further stimulation failed to restore the contractions.

Experiment 4. *Pithed Frog.*—Poison, 1/10 gramme to 1 c.c. Ringer's solution. The heart was stopped except for a tiny and feeble contraction of the auricle by application of the poison. A stimulus applied to the sinus as in Experiment 3 restored the heart beats. When the beats had attained their normal size, the application of more poison stopped the heart and stimulation now failed to arouse it.

Experiment 5. *Pithed Frog.*—Poison, 8 per cent. in Ringer's solution. The first effect of the poison was a gradual diminution in the size of the ventricular beats until they became the same size as the auricular beats and finally smaller. At this stage slow peristaltic action of the ventricle occurred, passing from base to apex. The ventricle also dropped beats and thus a marked irregularity of action was produced owing to a block at the auriculo-ventricular junction. On discontinuing the application of the poison the ventricle recovered itself.

More poison was applied and again the ventricle showed the same action as before and finally recovered a second time on the application being discontinued. A third application of the poison brought the ventricle to a standstill, the auricle continuing to beat. A 5-per-cent. solution of atropine was now applied.

There was no result for a little while and then the rate of the auricular contractions became much slower, and finally the rate sank from 39 to 12 per minute. The heart was not restored.

Experiment 6. *Pithed Frog.*—Atropine, 5 per cent. in Ringer's solution applied. The heart was now beating at 33 per minute. After 70 seconds an 8-per-cent. solution of the poison (Ringer's solution) was applied. The heart continued to beat at the same rate for about 40 seconds, and then the rate increased to 42 per minute, the beats becoming smaller; when the ventricular beats had become the same size as those of the auricle the rate was 33 per minute. The ventricle stopped in diastole, the auricle continuing to beat for a short time, when the heart finally stopped.

Experiments 7, 8, 9, 10, 11.—Five more experiments with the frog's heart were done, but these will not be given in detail as the results were exactly the same as has already been described.

Experiment 12. *Nerve Muscle Preparation of Frog. Pithed Frog.*—The preparation was made in the usual way. An induced current was used to stimulate the nerve. The solution of poison was applied to the muscle with a brush. Each time the poison was applied the muscle shortened slightly. The muscle was kept moist with the solution of poison until it failed to contract, when the nerve was stimulated. The electrodes were now applied to the muscle itself, but it failed to respond with the strongest current.

On the Origin of the Sertoli or Foot-cells of the Testis.

By C. E. Walker, Assistant-Director of Cancer Research Laboratories,
University of Liverpool, and Alice L. Embleton, B.Sc.

(Communicated by Dr. C. S. Sherrington, F.R.S. Received January 16,—
Read February 1, 1906.)

[Plates 5 and 6.]

The function of the Sertoli or foot-cells of the mammalian testis has frequently been described, and will not be dealt with in the present brief communication. Neither do we intend to deal with the later stages of the life-history of these cells, except in so far as to draw a parallel between them and the cells performing a similar function in the amphibia.

In the embryo testis of a mammal before the tubules are formed it is seen that a number of so-called male ova lie, singly or in groups of about four, among masses of cells, which we will for the moment designate as being of a more or less undifferentiated character. These undifferentiated cells are much smaller and of quite a different character to the male ova (see fig. 1).

At a little later stage we find that the wall of the tubule begins to appear. This wall is apparently actually in process of formation in parts of fig. 1, while in fig. 2 a tubule with a complete wall has been formed. We are convinced from a careful study of the stages of development that cells which form the wall of the tubule and those that are enclosed with the male ova inside the wall thus formed are identical or derived from the same immediate ancestors. As development goes on these cells become more and more differentiated until we reach the state of the tubule in the adult testis (fig. 3).